Supplementary material

Using wrist worn accelerometers to identify the sedentary impact of medicines with anticholinergic or sedative properties: a 12-month prospective analysis

Ty Stanford and Dot Dumuid

Table of contents

1 R setup

1.1 Pacakges

```
suppressPackageStartupMessages({
  require("compositions")

  require("dplyr")
  require("tidyr")
  require("readr")
  require("forcats")
  library("ggplot2")

  library("knitr")

  require("lme4")
  require("lmerTest")
  library("optimx")
  library("performance")
})
```

1.2 Session functions and constants

```
add_alpha <- function(col, alpha = 1) {
  apply(
    sapply(col, col2rgb) / 255, 2,
    function(x) rgb(x[1], x[2], x[3], alpha = alpha)
  )
}


stage_ins_col <- add_alpha(c("cyan", "magenta"), 0.25)
stage_out_col <-  add_alpha(c("cyan", "magenta"), 0.75)
names(stage_ins_col) <- names(stage_out_col) <- NULL


med_ins_col <- add_alpha(c("orange", "purple"), 0.25)
med_out_col <-  add_alpha(c("orange", "purple"), 0.75)
names(med_ins_col) <- names(med_out_col) <- NULL
```

```r
pal_use <- "Plasma" # "Temps", "Zissou 1"
plas_pal <- hcl.colors(n = 10, palette = pal_use, rev = FALSE)
sed_ins_col <- add_alpha(plas_pal, 0.25)
sed_out_col <-  add_alpha(plas_pal, 0.75)
names(sed_ins_col) <- names(sed_out_col) <- NULL
```

```r
pal_use <- "Viridis"
vir_pal <- hcl.colors(n = 11, palette = pal_use, rev = FALSE)
ach_ins_col <- add_alpha(vir_pal, 0.25)
ach_out_col <-  add_alpha(vir_pal, 0.75)
names(ach_ins_col) <- names(ach_out_col) <- NULL
```

2 Data processing

2.1 Read analysis data

```
sedach_dat <-
  read_rds("dat/sedach_dat.rds") %>%
  as_tibble(.)


sedach_dat$TrialStage <- fct_infreq(sedach_dat$TrialStage)
```

2.2 Create *ilr* coordinates from time-use categories

```
# these are the time-use compositions
time_use_cols <- paste0("tu_", c("sl", "sed", "lp", "mv"))
tu_dat <- sedach_dat[, time_use_cols]

# make isometric log ratios for compositional analysis of time-use composition
tu_comp <- acomp(tu_dat)
tu_ilrs <- as.data.frame(ilr(tu_comp))
D <- ncol(tu_ilrs)
colnames(tu_ilrs) <- paste0("ilr", 1:D)

# add ilrs to analysis dataset
sedach_dat <- bind_cols(sedach_dat, tu_ilrs)
colnames(sedach_dat)
```

```
 [1] "StudyID"    "TrialStage" "sed_score"  "ach_score"  "tu_sl"
 [6] "tu_sed"     "tu_lp"      "tu_mv"      "ilr1"       "ilr2"
[11] "ilr3"
```

3 Exploratory analysis

3.1 Correlation between predictor variables at trial stages

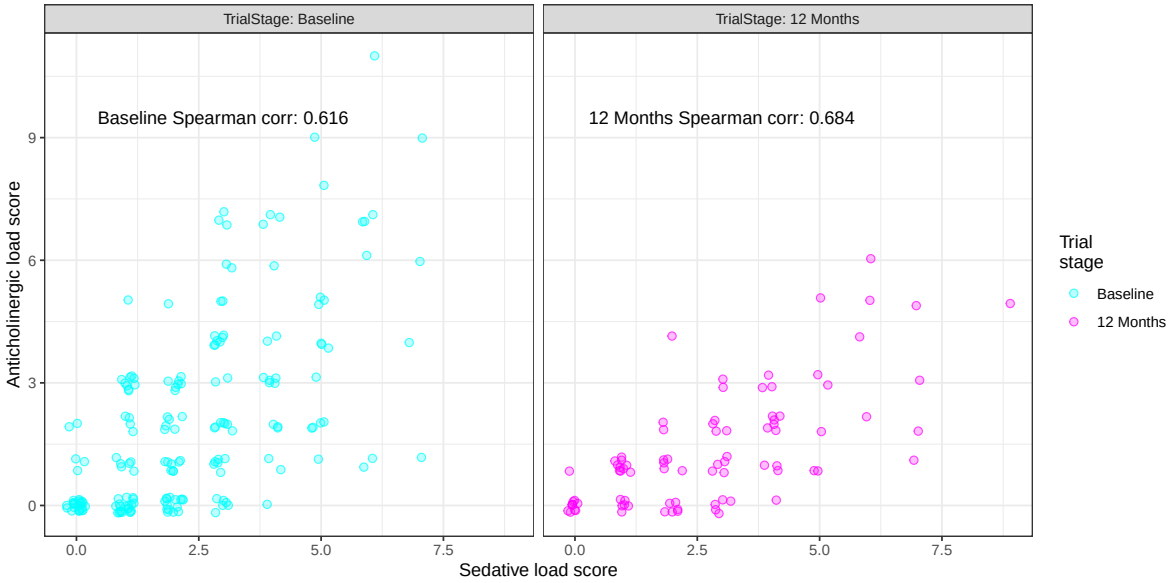


Figure 1: Scatterplot of sedentary and anticholinergic load scores at baseline and 12 months for each participant (complete data)

3.2 Change in predictor variables over trial stage

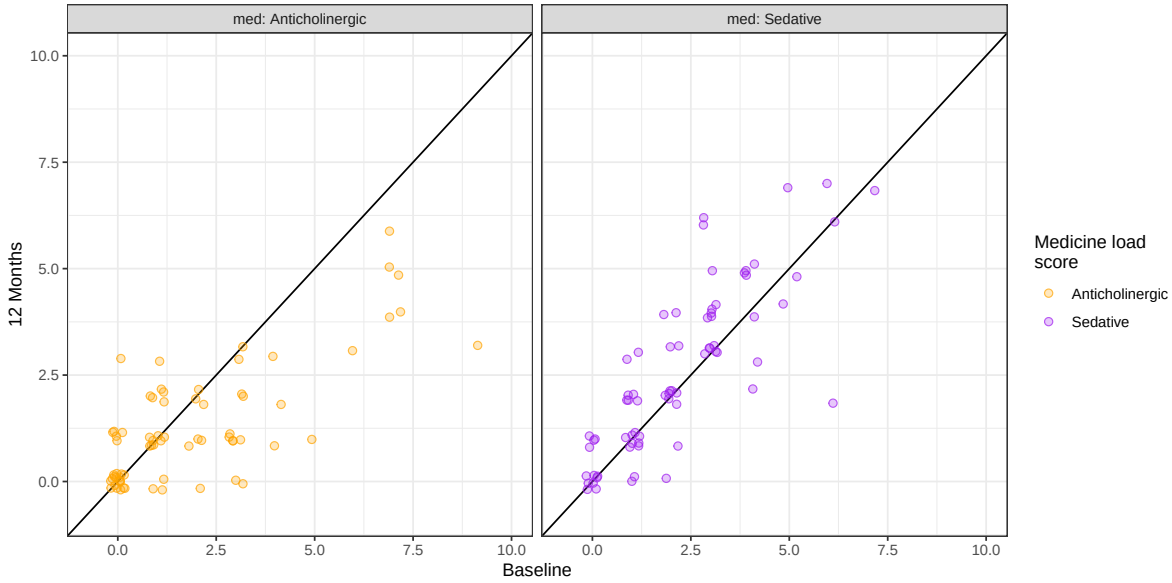


Figure 2: Scatterplot of baseline and 12 month sedentary and anticholinergic load scores for each participant (complete data)

3.3 Change in untransformed outcome variables over trial stage (by predictors)

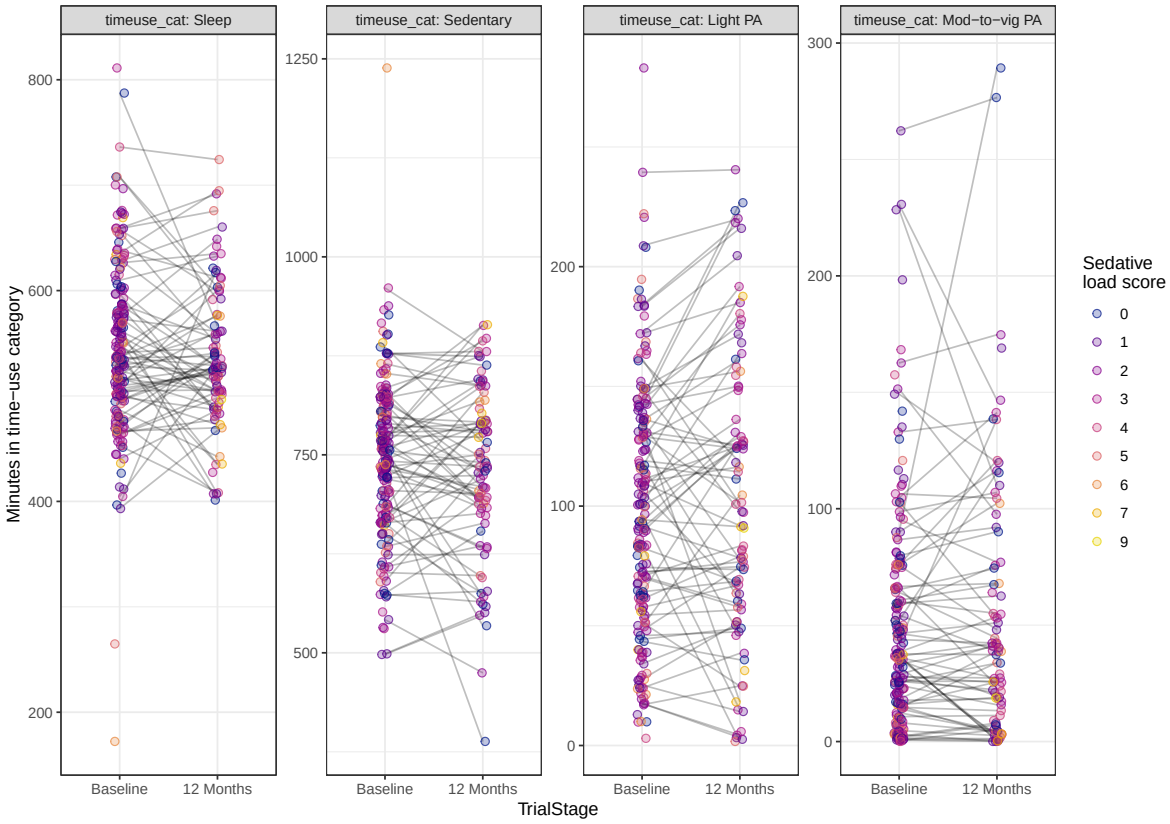


Figure 3: Minutes in each time-use category at baseline and 12 months for each participant (points coloured by sedentary load scores at trial stage)

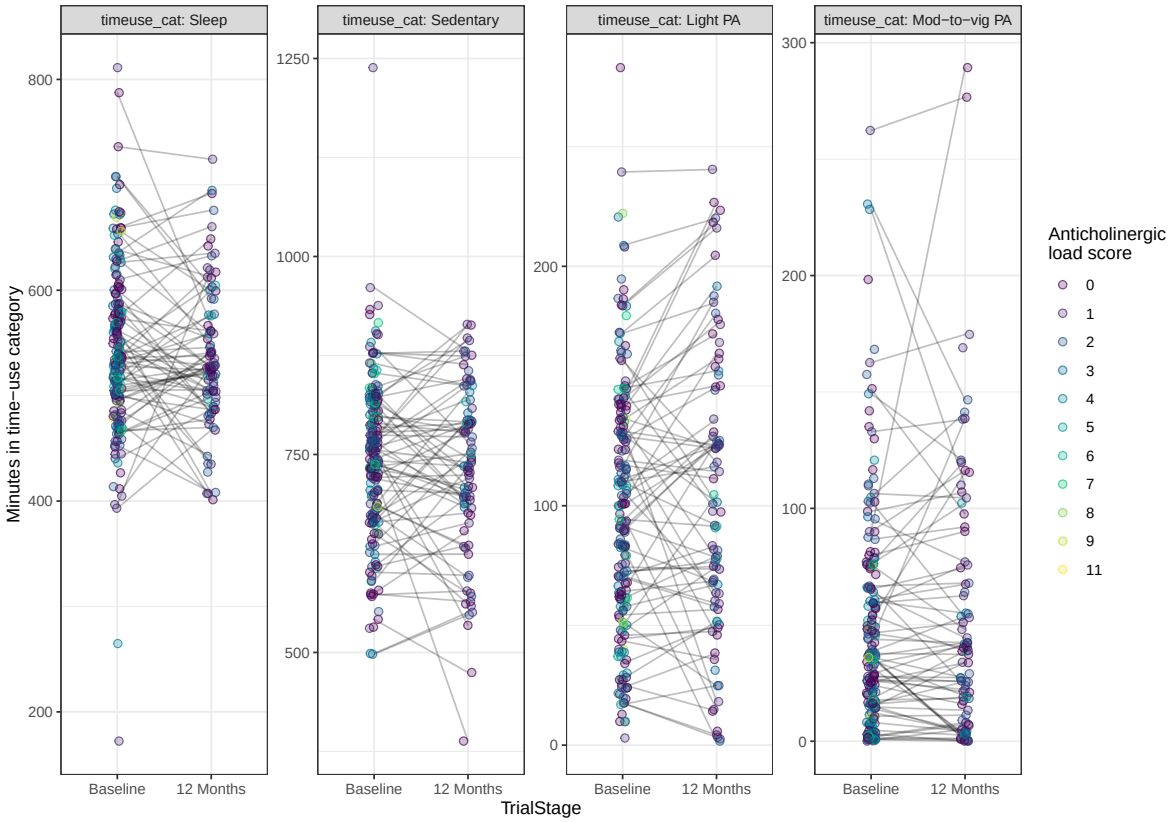


Figure 4: Minutes in each time-use category at baseline and 12 months for each participant (points coloured by anticholinergic load scores at trial stage)

3.4 Change in *ilr* transformed outcome variables over trial stage (by predictors)

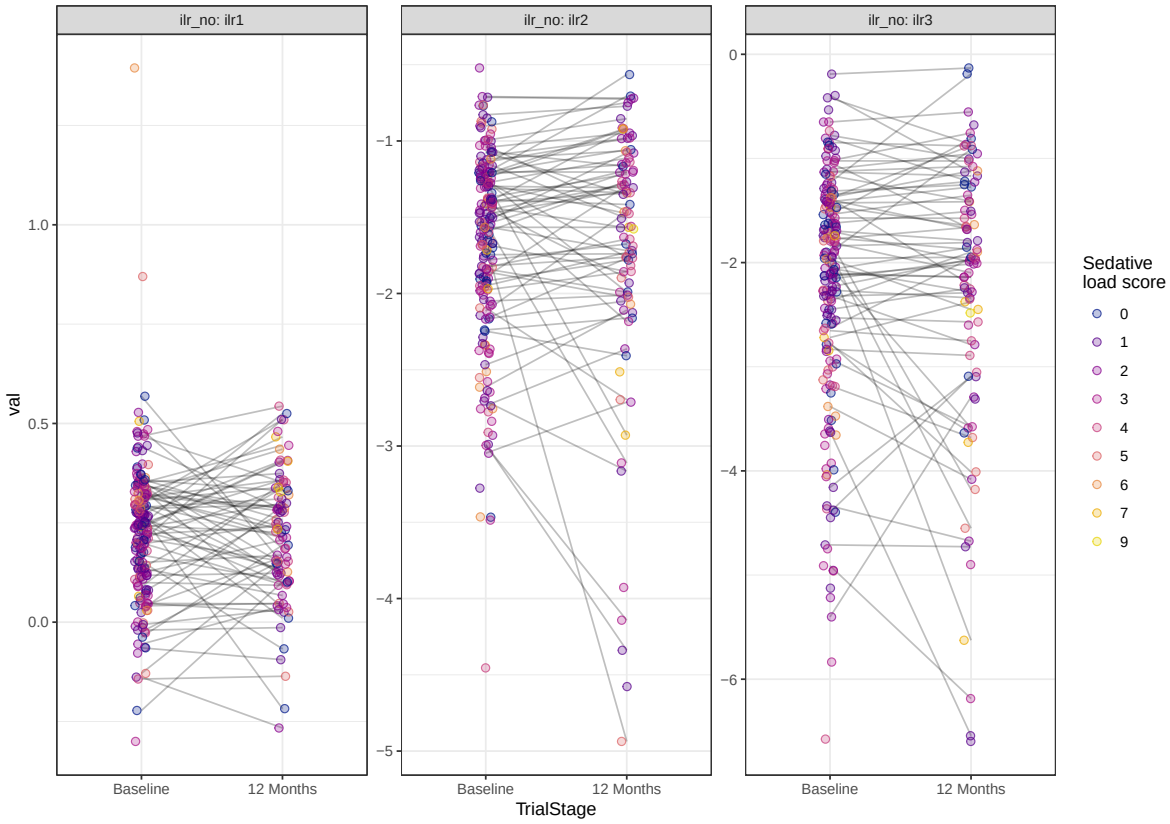


Figure 5: *ilr* values (transformed time-use category compositions) at baseline and 12 months for each participant (points coloured by sedentary load scores at trial stage)

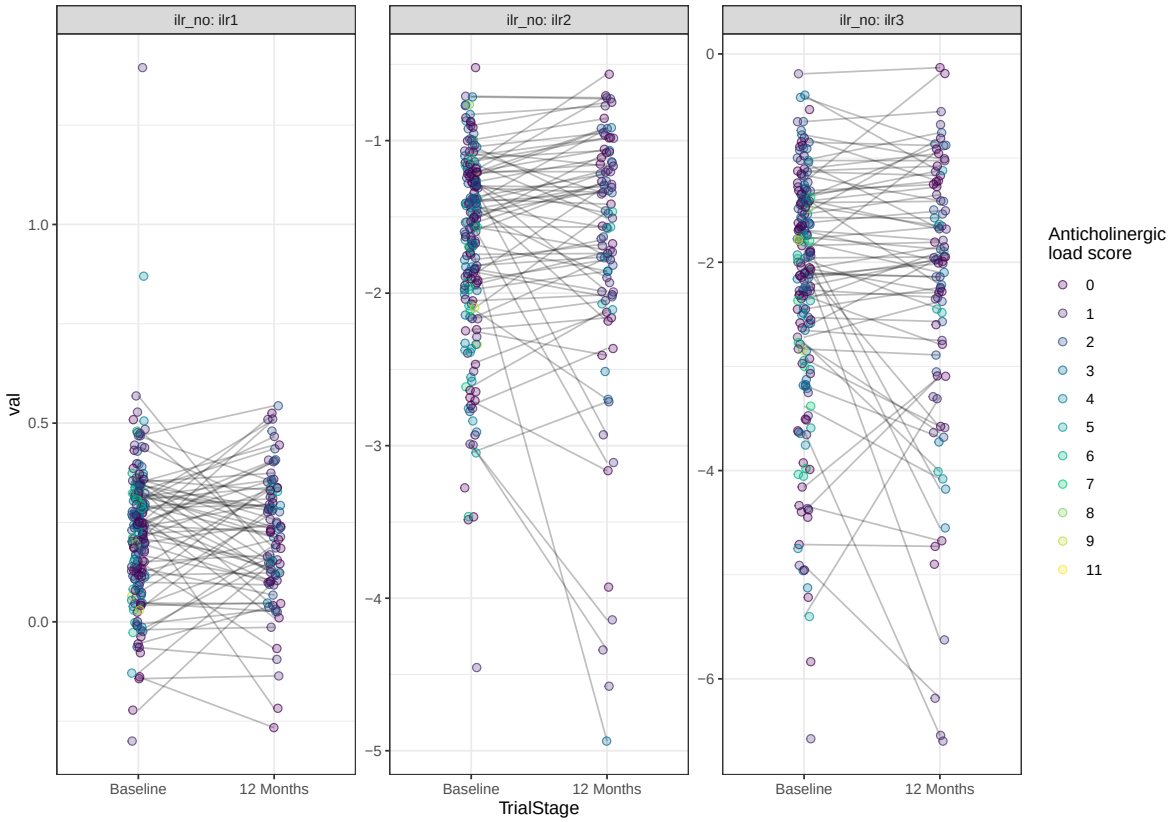


Figure 6: *ilr* values (transformed time-use category compositions) at baseline and 12 months for each participant (points coloured by anticholinergic load scores at trial stage)

4 Statistical modelling

4.1 Tansform data to long format

Creating "stacked" dataset.

```
# create stacked dataset for multi-level model, because the dependent variable will be
# the activity composition ILRS which are multivariate (there are 3 of them),
# and lmer can't handle multi-variate dependent variables.


dat_lng <-
  sedach_dat %>%
  dplyr::select(-starts_with("tu_")) %>%
  pivot_longer(
    .,
    cols = ilr1:ilr3,
    names_to = "ilr.no",
    values_to = "val"
  )
```

4.2 Stacked linear mixed effect model of *ilr* value on sedentary load scores

```r
# sedative load

set.seed(123)

mod_sed <-
  lmer(
    val ~ -1 +
      ilr.no +
      ilr.no:TrialStage + ilr.no:sed_score +
      ilr.no:TrialStage:sed_score +
      (0 + ilr.no | StudyID),
    data = dat_lng,
    control = lmerControl(
      optimizer = "Nelder_Mead",
      check.conv.singular =
        .makeCC(action = "ignore", tol = formals(isSingular)$tol)
    )
  )

summary(mod_sed)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula:
val ~ -1 + ilr.no + ilr.no:TrialStage + ilr.no:sed_score + ilr.no:TrialStage:sed_score +
    (0 + ilr.no | StudyID)
   Data: dat_lng
Control:
lmerControl(optimizer = "Nelder_Mead", check.conv.singular = .makeCC(action = "ignore",
    tol = formals(isSingular)$tol))

REML criterion at convergence: 1227.8

Scaled residuals:
    Min      1Q  Median      3Q     Max
-6.3074 -0.3876  0.0168  0.3902  4.6197

Random effects:
 Groups   Name        Variance  Std.Dev. Corr
```

```
 StudyID  ilr.noilr1 0.0009236 0.03039
          ilr.noilr2 0.4114020 0.64141  -0.85
          ilr.noilr3 1.4006466 1.18349  -0.98  0.94
 Residual            0.1077476 0.32825
Number of obs: 804, groups:  StudyID, 198

Fixed effects:
                                           Estimate Std. Error         df
ilr.noilr1                                 0.199874   0.040334 425.565897
ilr.noilr2                                -1.639237   0.076227 341.319951
ilr.noilr3                                -2.220218   0.124375 339.328326
ilr.noilr1:TrialStage12 Months            -0.034907   0.072617 426.894903
ilr.noilr2:TrialStage12 Months             0.010617   0.080827 575.618614
ilr.noilr3:TrialStage12 Months             0.183208   0.089304 485.472133
ilr.noilr1:sed_score                       0.010558   0.013743 426.072722
ilr.noilr2:sed_score                      -0.025484   0.023587 462.334778
ilr.noilr3:sed_score                      -0.013386   0.036974 533.790689
ilr.noilr1:TrialStage12 Months:sed_score   0.008858   0.022371 426.945020
ilr.noilr2:TrialStage12 Months:sed_score  -0.031929   0.025733 596.149168
ilr.noilr3:TrialStage12 Months:sed_score  -0.137570   0.029644 518.882373
                                          t value Pr(>|t|)
ilr.noilr1                                  4.955 1.04e-06 ***
ilr.noilr2                                -21.505  < 2e-16 ***
ilr.noilr3                                -17.851  < 2e-16 ***
ilr.noilr1:TrialStage12 Months             -0.481   0.6310
ilr.noilr2:TrialStage12 Months              0.131   0.8955
ilr.noilr3:TrialStage12 Months              2.052   0.0408 *
ilr.noilr1:sed_score                        0.768   0.4428
ilr.noilr2:sed_score                       -1.080   0.2805
ilr.noilr3:sed_score                       -0.362   0.7175
ilr.noilr1:TrialStage12 Months:sed_score    0.396   0.6923
ilr.noilr2:TrialStage12 Months:sed_score   -1.241   0.2152
ilr.noilr3:TrialStage12 Months:sed_score   -4.641 4.40e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            ilr.n1 ilr.n2 ilr.n3 il.1:TS12M il.2:TS12M il.3:TS12M il.1:_ il.2:_
ilr.noilr2  -0.051
ilr.noilr3  -0.070  0.736
ilr.1:TS12M -0.552  0.001  0.002
ilr.2:TS12M  0.002 -0.305 -0.031 -0.001
ilr.3:TS12M  0.005 -0.046 -0.208 -0.012      0.145
```

```
ilr.nlr1:s_ -0.797  0.029  0.042  0.441     -0.002     -0.006
ilr.nlr2:s_  0.032 -0.733 -0.478 -0.001      0.285      0.061     -0.039
ilr.nlr3:s_  0.048 -0.497 -0.708 -0.003      0.043      0.219     -0.059  0.672
i.1:TS12M:_  0.488 -0.004 -0.006 -0.802      0.001      0.011     -0.612  0.005
i.2:TS12M:_ -0.006  0.334  0.098  0.001     -0.799     -0.138      0.008 -0.472
i.3:TS12M:_ -0.014  0.139  0.296  0.011     -0.132     -0.793      0.019 -0.200
            il.3:_ i.1:TS12M: i.2:TS12M:
ilr.noilr2
ilr.noilr3
ilr.1:TS12M
ilr.2:TS12M
ilr.3:TS12M
ilr.nlr1:s_
ilr.nlr2:s_
ilr.nlr3:s_
i.1:TS12M:_  0.009
i.2:TS12M:_ -0.147 -0.003
i.3:TS12M:_ -0.438 -0.016      0.205
```

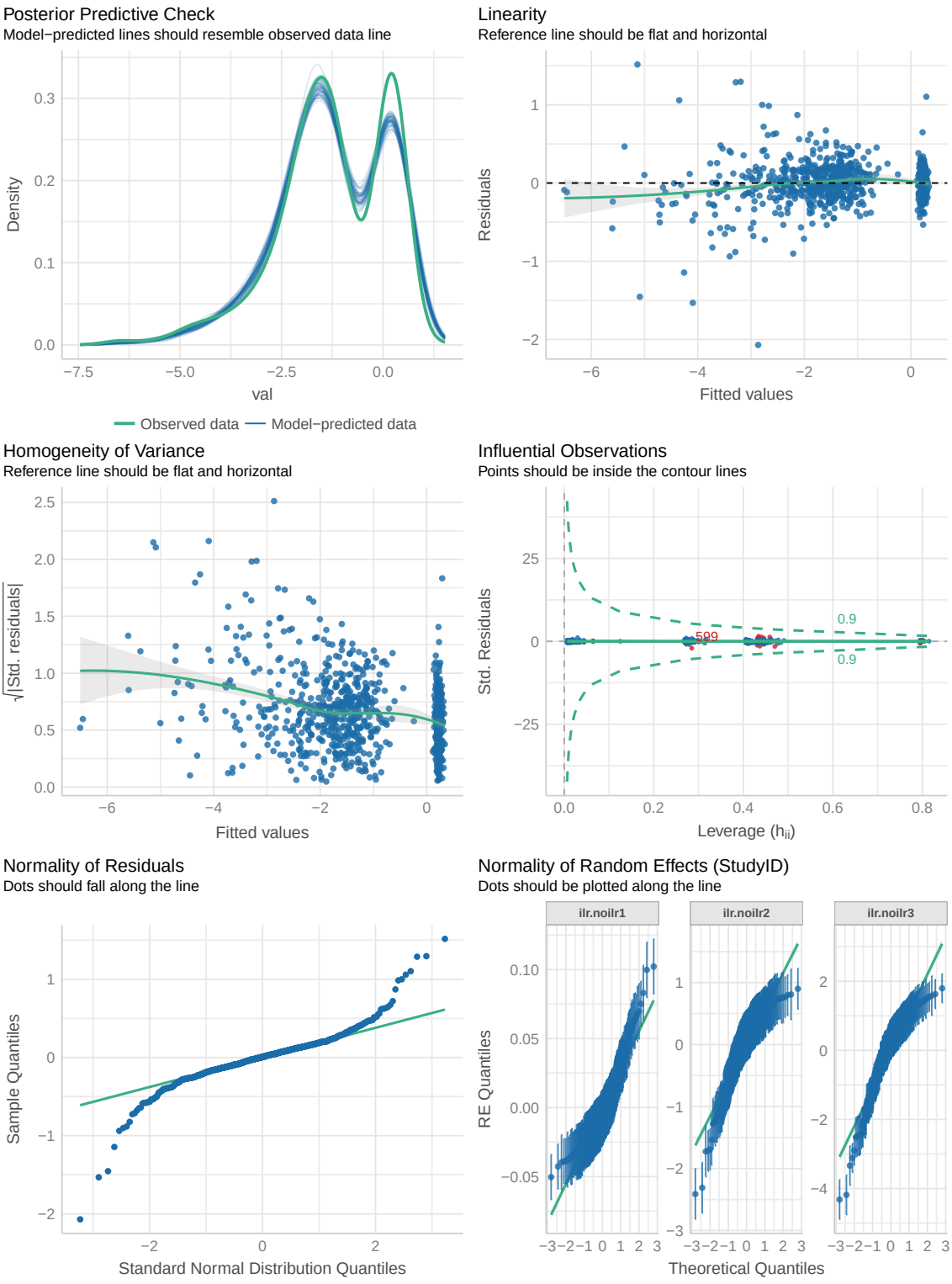
```
car::Anova(mod_sed, test.statistic = "F", type = "III")
```

```
Analysis of Deviance Table (Type III Wald F tests with Kenward-Roger df)

Response: val
                                F Df Df.res    Pr(>F)
ilr.no                  160.1101  3 327.02 < 2.2e-16 ***
ilr.no:TrialStage         1.4743  3 341.83 0.2213077
ilr.no:sed_score          0.6487  3 361.66 0.5842196
ilr.no:TrialStage:sed_score   7.2106  3 364.88 0.0001031 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
check_model(
  mod_sed,
  check = c("reqq", "qq", "linearity", "homogeneity", "outliers", "pp_check")
)
```

```
Variable `Component` is not in your data frame :/
```


Posterior Predictive Check
Model−predicted lines should resemble observed data line
Density
val
Observed data
Model−predicted data
Linearity
Reference line should be flat and horizontal
Residuals
Fitted values
Homogeneity of Variance
Reference line should be flat and horizontal
√|Std. residuals|
Fitted values
Influential Observations
Points should be inside the contour lines
Std. Residuals
Leverage (hii)
0.9
0.9
599
Normality of Residuals
Dots should fall along the line
Sample Quantiles
Standard Normal Distribution Quantiles
Normality of Random Effects (StudyID)
Dots should be plotted along the line
ilr.noilr1
ilr.noilr2
ilr.noilr3
RE Quantiles
Theoretical Quantiles

4.3 Stacked linear mixed effect model of *ilr* value on anticholinergic load scores

```r
# Anti-cholinergic load


mod_ach <-
  lmer(
    val ~
      -1 + ilr.no +
      ilr.no:TrialStage + ilr.no:ach_score +
      TrialStage:ach_score:ilr.no +
      (0 + ilr.no | StudyID),
    data = dat_lng,
    control = lmerControl(
      optimizer = "bobyqa",
      check.conv.singular =
        .makeCC(action = "ignore", tol = formals(isSingular)$tol)
    )
  )

summary(mod_ach)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula:
val ~ -1 + ilr.no + ilr.no:TrialStage + ilr.no:ach_score + TrialStage:ach_score:ilr.no +
    (0 + ilr.no | StudyID)
   Data: dat_lng
Control:
lmerControl(optimizer = "bobyqa", check.conv.singular = .makeCC(action = "ignore",
    tol = formals(isSingular)$tol))

REML criterion at convergence: 1247

Scaled residuals:
    Min      1Q  Median      3Q     Max
-6.2564 -0.3747  0.0189  0.3782  4.7557

Random effects:
 Groups   Name       Variance Std.Dev. Corr
 StudyID  ilr.noilr1 0.001013 0.03183
```

```
          ilr.noilr2 0.409168 0.63966  -0.86
          ilr.noilr3 1.400289 1.18334  -0.98  0.94
 Residual             0.112326 0.33515
Number of obs: 804, groups:  StudyID, 198

Fixed effects:
                                            Estimate Std. Error         df
ilr.noilr1                                  0.215239   0.033217 426.518327
ilr.noilr2                                 -1.667481   0.063167 304.362549
ilr.noilr3                                 -2.220319   0.103818 286.192051
ilr.noilr1:TrialStage12 Months             -0.018859   0.060162 428.007291
ilr.noilr2:TrialStage12 Months             -0.038640   0.067045 580.546065
ilr.noilr3:TrialStage12 Months             -0.040534   0.074608 489.261934
ilr.noilr1:ach_score                        0.004733   0.010885 427.364569
ilr.noilr2:ach_score                       -0.017527   0.017653 497.079369
ilr.noilr3:ach_score                       -0.019626   0.027057 584.019510
ilr.noilr1:TrialStage12 Months:ach_score    0.011631   0.027822 428.038825
ilr.noilr2:TrialStage12 Months:ach_score   -0.038667   0.032571 601.765078
ilr.noilr3:TrialStage12 Months:ach_score   -0.115156   0.038095 524.429410
                                           t value Pr(>|t|)
ilr.noilr1                                   6.480 2.54e-10 ***
ilr.noilr2                                 -26.398  < 2e-16 ***
ilr.noilr3                                 -21.387  < 2e-16 ***
ilr.noilr1:TrialStage12 Months              -0.313  0.75408
ilr.noilr2:TrialStage12 Months              -0.576  0.56462
ilr.noilr3:TrialStage12 Months              -0.543  0.58718
ilr.noilr1:ach_score                         0.435  0.66392
ilr.noilr2:ach_score                        -0.993  0.32125
ilr.noilr3:ach_score                        -0.725  0.46852
ilr.noilr1:TrialStage12 Months:ach_score    0.418  0.67610
ilr.noilr2:TrialStage12 Months:ach_score   -1.187  0.23564
ilr.noilr3:TrialStage12 Months:ach_score   -3.023  0.00263 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            ilr.n1 ilr.n2 ilr.n3 il.1:TS12M il.2:TS12M il.3:TS12M il.1:_ il.2:_
ilr.noilr2  -0.056
ilr.noilr3  -0.074  0.747
ilr.1:TS12M -0.549  0.001  0.002
ilr.2:TS12M  0.001 -0.297 -0.027 -0.001
ilr.3:TS12M  0.005 -0.040 -0.196 -0.013      0.155
ilr.nlr1:c_ -0.663  0.020  0.030  0.365     -0.002     -0.005
```

```
ilr.nlr2:c_  0.024 -0.568 -0.338 -0.001      0.250      0.053     -0.035
ilr.nlr3:c_  0.037 -0.363 -0.532 -0.003      0.039      0.195     -0.056  0.635
i.1:TS12M:_  0.258  0.003  0.003 -0.673      0.001      0.011     -0.389 -0.004
i.2:TS12M:_  0.004  0.070 -0.052  0.001     -0.668     -0.121     -0.006 -0.135
i.3:TS12M:_  0.007 -0.074 -0.026  0.010     -0.116     -0.657     -0.009  0.118
            il.3:_ i.1:TS12M: i.2:TS12M:
ilr.noilr2
ilr.noilr3
ilr.1:TS12M
ilr.2:TS12M
ilr.3:TS12M
ilr.nlr1:c_
ilr.nlr2:c_
ilr.nlr3:c_
i.1:TS12M:_ -0.005
i.2:TS12M:_  0.090 -0.003
i.3:TS12M:_  0.032 -0.019      0.227
```

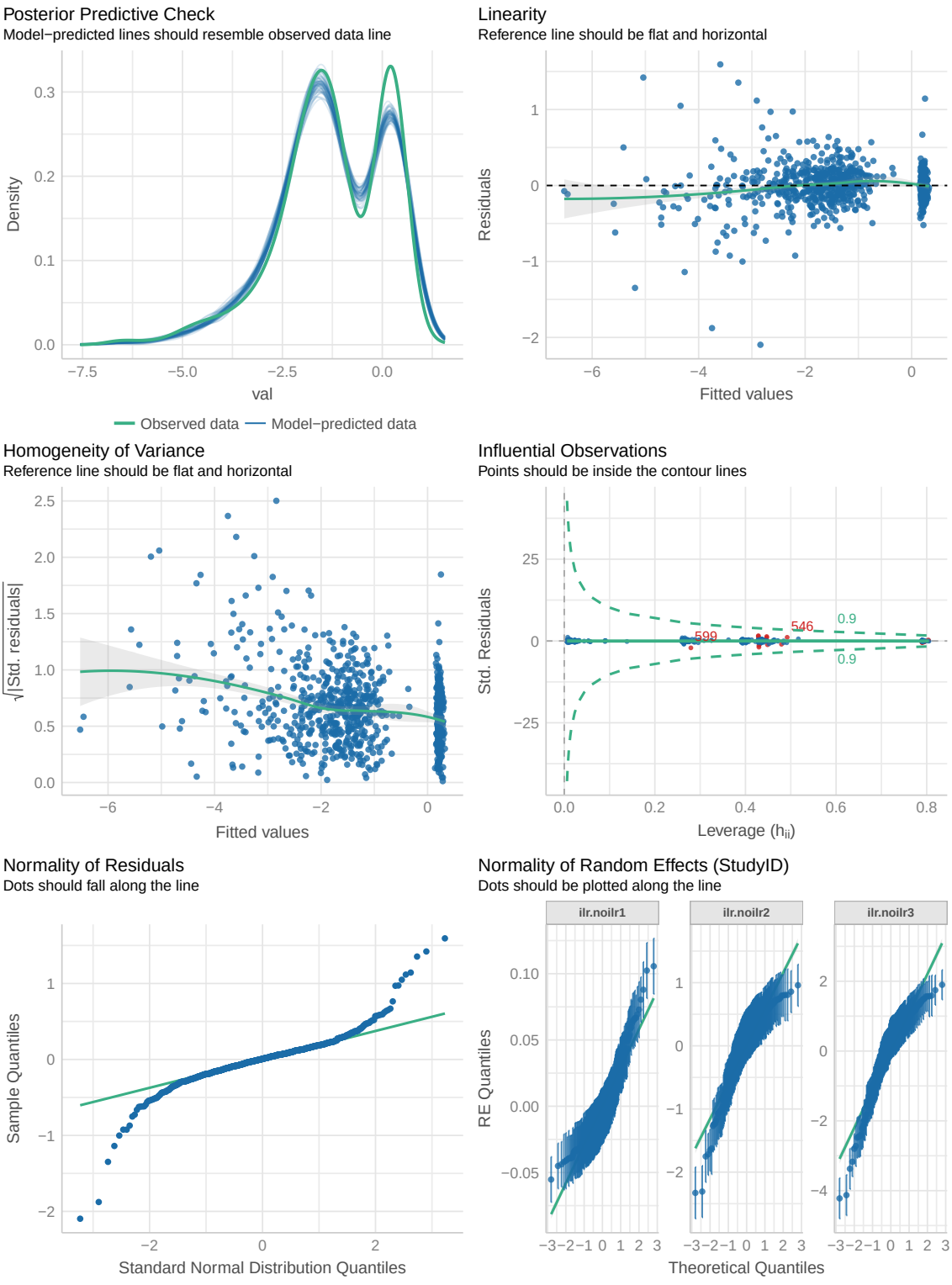
```
car::Anova(mod_ach, test.statistic = "F", type = "III")
```

```
Analysis of Deviance Table (Type III Wald F tests with Kenward-Roger df)

Response: val
                                  F Df Df.res Pr(>F)
ilr.no                     240.2913  3 314.59 <2e-16 ***
ilr.no:TrialStage            0.2142  3 346.41 0.8866
ilr.no:ach_score             0.3806  3 369.90 0.7670
ilr.no:TrialStage:ach_score  3.1629  3 378.29 0.0246 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
check_model(
  mod_ach,
  check = c("reqq", "qq", "linearity", "homogeneity", "outliers", "pp_check")
)
```

```
Variable `Component` is not in your data frame :/
```


Posterior Predictive Check
Model−predicted lines should resemble observed data line
Density
val
Observed data
Model−predicted data
Linearity
Reference line should be flat and horizontal
Residuals
Fitted values
Homogeneity of Variance
Reference line should be flat and horizontal
√|Std. residuals|
Fitted values
Influential Observations
Points should be inside the contour lines
Std. Residuals
Leverage (hii)
546
599
0.9
0.9
Normality of Residuals
Dots should fall along the line
Sample Quantiles
Standard Normal Distribution Quantiles
Normality of Random Effects (StudyID)
Dots should be plotted along the line
ilr.noilr1
ilr.noilr2
ilr.noilr3
RE Quantiles
Theoretical Quantiles

4.4 Predictions from model

```
newd1 <-
  expand.grid(
    ilr.no = c("ilr1", "ilr2", "ilr3"),
    TrialStage = c("Baseline", "12 Months"),
    score = 4
  )
rownames(newd1) <- apply(newd1, 1, paste, collapse = "_")
newd2 <-
  expand.grid(
    ilr.no = c("ilr1", "ilr2", "ilr3"),
    TrialStage = c("12 Months", "Baseline"),
    score = 2
  )
rownames(newd2) <- apply(newd2, 1, paste, collapse = "_")

newd <- rbind(newd1, newd2)

newd <-
  newd %>%
  dplyr::filter(
    (TrialStage == "Baseline" & score == 2) |
      (TrialStage == "12 Months" & score == 4)
  )

newd_sed <-
  newd %>%
  rename(sed_score = score)

newd_ach <-
  newd %>%
  rename(ach_score = score)



get_sed_diff <- function(.) {
  pred_val <- predict(., newdata = newd_sed, re.form = NA)
  pred_newd <- cbind.data.frame(pred_val, newd_sed)
  pred_newd_w <- spread(pred_newd, key = ilr.no, value = pred_val)
  ilr_cols <- grepl("ilr", colnames(pred_newd_w))
```

```r
  time_use <- 1440 * unclass(ilrInv(pred_newd_w[, ilr_cols]))
  colnames(time_use) <- c("sl", "sed", "lp", "mv")
  # return(time_use[2, "sed"] - time_use[1, "sed"])
  return(time_use[2, ] - time_use[1, ])
}

cat(
  "This is expected change in minutes to the time-use composition\n",
  "when going from sed load = 2 to sed load = 4 from baseline to 12 months.\n"
)
get_sed_diff(mod_sed) %>%
  tibble(time_use_cat = names(.), minutes = .) %>%
  kable(., digits = 1)



get_ach_diff <- function(.) {
  pred_val <- predict(., newdata = newd_ach, re.form = NA)
  pred_newd <- cbind.data.frame(pred_val, newd_ach)
  pred_newd_w <- spread(pred_newd, key = ilr.no, value = pred_val)
  ilr_cols <- grepl("ilr", colnames(pred_newd_w))
  time_use <- 1440 * unclass(ilrInv(pred_newd_w[, ilr_cols]))
  colnames(time_use) <- c("sl", "sed", "lp", "mv")
  # return(time_use[2, "sed"] - time_use[1, "sed"])
  return(time_use[2, ] - time_use[1, ])
}

cat(
  "This is expected change in minutes to the time-use composition\n",
  "when going from anticholinergic load = 2 to sed load = 4\n",
  "from baseline to 12 months.\n"
)
get_ach_diff(mod_ach) %>%
  tibble(time_use_cat = names(.), minutes = .) %>%
  kable(., digits = 1)
```

```
This is expected change in minutes to the time-use composition
 when going from sed load = 2 to sed load = 4 from baseline to 12 months.
```

time_use_cat	minutes
sl	0.1
sed	24.1
lp	-14.4
mv	-9.8

```
This is expected change in minutes to the time-use composition
 when going from anticholinergic load = 2 to sed load = 4
 from baseline to 12 months.
```

time_use_cat	minutes
sl	-4.3
sed	35.3
lp	-18.8
mv	-12.2

5 Session info

```
format(Sys.time(), '%d-%b-%Y')
```

```
[1] "01-Mar-2023"
```

```
sessionInfo()
```

```
R version 4.2.2 (2022-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19044)

Matrix products: default

locale:
[1] LC_COLLATE=English_Australia.utf8  LC_CTYPE=English_Australia.utf8
[3] LC_MONETARY=English_Australia.utf8 LC_NUMERIC=C
[5] LC_TIME=English_Australia.utf8

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] performance_0.10.2 optimx_2022-4.30   lmerTest_3.1-3     lme4_1.1-31
 [5] Matrix_1.5-3       knitr_1.42         ggplot2_3.4.1      forcats_1.0.0
 [9] readr_2.1.4        tidyr_1.3.0        dplyr_1.1.0        compositions_2.0-5

loaded via a namespace (and not attached):
 [1] ggrepel_0.9.3       Rcpp_1.0.10         lattice_0.20-45
 [4] digest_0.6.31       utf8_1.2.3          R6_2.5.1
 [7] backports_1.4.1     evaluate_0.20       pillar_1.8.1
[10] rlang_1.0.6         rstudioapi_0.14     minqa_1.2.5
[13] see_0.7.4           car_3.1-1           nloptr_2.0.3
[16] rmarkdown_2.20      labeling_0.4.2      splines_4.2.2
[19] munsell_0.5.0       broom_1.0.3         compiler_4.2.2
[22] numDeriv_2016.8-1.1 xfun_0.37           pkgconfig_2.0.3
[25] mgcv_1.8-41         htmltools_0.5.4     insight_0.19.0
[28] tidyselect_1.2.0    tibble_3.1.8        tensorA_0.36.2
[31] fansi_1.0.4         tzdb_0.3.0          withr_2.5.0
```

```
[34] MASS_7.3-58.1       grid_4.2.2          nlme_3.1-160
[37] bayesm_3.1-5        jsonlite_1.8.4      gtable_0.3.1
[40] lifecycle_1.0.3     magrittr_2.0.3      bayestestR_0.13.0
[43] scales_1.2.1        datawizard_0.6.5    cli_3.6.0
[46] carData_3.0-5       farver_2.1.1        robustbase_0.95-0
[49] ellipsis_0.3.2      generics_0.1.3      vctrs_0.5.2
[52] boot_1.3-28         tools_4.2.2         glue_1.6.2
[55] DEoptimR_1.0-11     purrr_1.0.1         hms_1.1.2
[58] abind_1.4-5         pbkrtest_0.5.2      parallel_4.2.2
[61] fastmap_1.1.0       yaml_2.3.7          colorspace_2.1-0
[64] patchwork_1.1.2
```